

REMARKS/ARGUMENTS**I. Withdrawal of Rejections**

Applications acknowledge and thank the Examiner for consideration of their arguments and withdrawal of the following rejections:

- Claims 1, 2, 7 - 9, 11, 34 and 35 under 35 U.S.C. § 103(a) as being unpatentable over Xiao et al. in view of Haase;
- Claim 10 under 35 U.S.C. § 103(a) as being unpatentable over Xiao et al. in view of Haase and further in view of Smith et al.;
- Claims 1, 16, 36 and 37 under 35 U.S.C. § 103(a) as being unpatentable over Xiao et al. in view of Haase and further in view of Kumar et al.;
- Claims 30 and 31 under 35 U.S.C. § 103(a) as being unpatentable over Xiao et al. in view of Haase and further in view of Le Febre et al.;
- Claims 32 and 33 under 35 U.S.C. § 103(a) as being unpatentable over Xiao et al. in view of Haase and Le Febre et al. and further in view of Kumar et al.;

II. Claim Rejections under 35 U.S.C. §103**A. Xiao et al. in view of Henry et al.**

On page 3 of the Office action, the Examiner rejected claims 1, 2, 7 - 9, 11, 31, 34, 35 and 38 under 35 U.S.C. 103(a) as allegedly unpatentable over Xiao et al. ("Xiao", US 20020164824) in view of Henry et al. ("Henry", US 2002/0176800). The Examiner states, "Xiao et al. disclose an array of capillary tubes, each capillary tube having a first end, a second end, and an inner surface having extraction agents immobilized thereto. The extraction agents (e.g. proteins and antibodies) are configured to bind specific biomolecules (e.g. proteins, virus). The capillary tube disclosed by Xiao et al. differs from the claimed invention in that Xiao et al. do not disclose that the capillary tube is coiled."

The Examiner goes on to state, "Henry et al. disclose a capillary for conducting liquid chromatography wherein the capillary is coiled or spiral in shape. The coil radius of the capillary can be 1 cm. The reference discloses that the coiling consolidates the lengths of capillaries into small spaces for convenient shipping and temperature control. In light of the disclosure of Henry et al., it would have been obvious to coil the capillary disclosed by Xiao et al. having a coil radius of 1 cm." Applicants respectfully traverse the rejection.

1. A person having ordinary skill in the art could not arrive at the claimed invention based on the teachings of Xiao and Henry.

Henry teaches a **packed** miniature liquid chromatography column having a curved or coiled configuration¹. Henry makes reference to the historic teaching that bending or coiling diminishes column efficiency and expresses concern that coiling or curving an LC column would negatively impact bed uniformity and thus, column performance². However, when Henry compares chromatographic efficiency between straight, U-shape and coiled fused silica column configurations, all three configurations perform equally well³.

To produce the U-shaped and coiled columns, Henry fills straight columns with a chromatographic medium and then bends the columns either into a U-shape or coils⁴. Although Henry states that the columns can be filled subsequent to bending⁵, Henry does not do it this way. Instead, Henry fills the column prior to bending.

Technically, there is an enormous difference between filling the columns before bending and filling the columns after bending. It is extremely difficult to coil an **open** fused silica column, especially to the small bend radius of less than 3 cm recited in the claims. The presence of beads in Henry's column facilitated tight coiling by allowing the bending stress to be distributed evenly along the curve of the coil. This concept is similar to constructing an arch where the forces are distributed along the entire arch. Furthermore, fused silica columns are quite fragile and often possesses weak spots. Henry confirms that fused silica tubing is fragile and subject to breakage either before or during column installation⁶. The tubing can break at these weak spots at the time of coiling, or the weak spot can cause the coiled tubing to break at a later time. However, when a weak spot in the capillary is supported by the presence of the beads, the forces are evenly distributed along the length of the capillary coil, making it less likely to break.

Applicants submit that Henry did not coil the columns to a bend radius of 2 cm before filling because it was extremely difficult to do so, if not impossible. Although Henry states that the columns can be filled subsequent to bending, it is merely a statement. Henry did not actually reduce this method to practice. 35 U.S.C. 112 states, "The specification shall contain a written description

¹ Henry, abstract.

² Henry, paragraphs [0008] and [0009].

³ Henry, paragraph [0033], Figure 7.

⁴ Henry, paragraph [0064].

⁵ Henry, paragraph [0065].

⁶ Henry, paragraph [0007].

of the invention, and of **the manner and process of making and using it**, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.” (emphasis added) Henry has not disclosed the process of making an **open** tubular capillary having a bend radius of less than 3 cm. Again, Henry merely states that the capillary can be filled subsequent to bending. It is also worth noting that although Xiao’s invention would have benefited from coiling the capillaries, Xiao does not teach coiled capillaries.

In contrast to the dearth of enablement offered by Henry, Applicants’ specification describes methods for tightly coiling the capillaries without the introduction of nicks or other breakage⁷. These methods include:

- Avoidance of twisting while coiling the capillaries
- Use of a thick capillary coating, preferably polyimide
- Minimal exposure to high pH conditions
- Comparison of capillary coiling ability between vendors
- Pre-testing the coilability of particular lots or sections of tubing
- Avoidance of unnecessary handling of the fused silica tubing⁸

In order for an invention to be considered obvious, it is necessary that a person having ordinary skill in the art could arrive at the invention based on the cited references. Applicants argue that a person having ordinary skill in the art would not be able to arrive at the claimed invention based on the teachings of Xiao and Henry because:

- 1) Applicants encountered complex technical obstacles when tightly coiling open fused silica columns,
- 2) open tubular capillaries having a small bend radius (less than 3 cm) are against conventional wisdom in the art, and
- 3) multiple references teach away from tightly coiled open fused silica capillaries with a small bend radius as explained below.

Henry merely states that columns can conceivably be bent before filling them with chromatographic medium, he did not show that it was done that way. Henry did not reduce it to practice and in no way disclosed the manner and process of making and using of the same. Applicants’ position, in contrast,

⁷ Applicant’s specification, pages 58, line 23 through page 59, line 27.

⁸ Applicant’s specification, Example 53, pages 114 – 115.

describes actual methods of tight coiling of the capillaries without breakage.

2. Open tubular capillaries having a bend radius of less than 3 cm are contrary to accepted wisdom in the art.

According to section 2145 of the MPEP, proceeding contrary to accepted wisdom in the art is evidence of non-obviousness. It is Applicants' position that the claimed capillaries having a bend radius of less than 3 cm are contrary to accepted wisdom in the art.

a. Polymicro Technologies

Polymicro Technologies, a leading supplier of fused silica capillary tubing, teach away from the tight coiling of fused silica capillaries. In their book, "The Book on the Technologies of Polymicro", (copyright 2002), Polymicro recommends against tight coiling. Polymicro provides a table of Applied Bending Stress, measured in kpsi for fused silica capillary tubing. Applicants included this table as Figure 22 of their specification. The table (which is also inserted below) gives applied bending stress as a function of bend radius (mm) and total outer diameter (μm). According to Polymicro Technologies, a kpsi of over 100 exceeds capillary break strength and is not recommended.

In Example 51 from Applicants' specification, a capillary having an outer diameter of $360\ \mu\text{m}$ was coiled inside a plastic ring having an inside diameter of 0.55 inches (approximately 1.4 cm). This corresponds to a bend radius of 0.7 cm (7 mm). According to Polymicro Technologies, these capillaries had a kpsi of between 170 and 213, a value well exceeding the recommended 100 kpsi. Therefore, the bend radius of the coiled capillaries used successfully by Applicants in Example 51 was recommended against by Polymicro. Therefore, Polymicro Technologies teaches away from the claimed invention.

b. Applicants' specification

Throughout the specification, Applicants repeatedly make reference to the fact that the tight coiling of capillaries is against conventional wisdom.

1. The following passage from Applicants' specification describes the long-held belief that tight coils of fused silica capillary tubing are not recommended due to the bending stress⁹.

While the instant disclosure identifies a number of advantages resulting from the use of the tightly coiled fused silica extraction capillaries, there is a limit to how tightly a fused silica capillary can be coiled or bent without resulting in breakage or other impairment of function. This is because bending the capillary tubing results in applied bending stress in the tubing which will eventually cause the tubing to break if the bending radius is too tight. In an extreme case where the bending radius is very small, breakage occurs at the time of bending. However, at less extreme bending radii the tubing does not initially break, but over the course of time the bending stress will result in a breakdown of the capillary that will impact performance. Thus, although it has been recognized that fused silica capillary tubing can be bent to some degree, e.g., in loose, high bend radius loops, it has been thought that this type of tubing should not be wound into tighter coils of lower bend radius because this would presumably result in an applied bending stress exceeding the capillary break strength. This perceived inability to tightly coil fused silica capillary tubing would dissuade those of skill in the art from attempting to construct some of the compact extraction capillary devices of the present invention. However, the instant inventors have discovered that fused silica capillary tubing can be coiled substantially tighter than previously believed, while retaining the ability to function as an extraction device for extended periods of times. By employing these tightly coiled capillaries it is possible to create compact, tightly coiled extraction capillaries for use in extraction devices of the invention that are stable for extended periods.

2. Applicants' specification refers to the applied bending stress table published by Polymicro Technologies and includes Polymicro's table as Figure 22 (see below).

⁹ Applicant's specification, page 55, lines 1 – 23.

Applied Bending Stress (kpsi)

Total OD (μm)	Bend Radius (mm)															
	4	6	8	10	15	20	25	30	40	50	60	80	100	130	160	200
90	87	58	43	35	23	17	14	12	9	7	6	4	3	3	2	2
105	106	71	53	43	28	21	17	14	11	9	7	5	4	3	3	2
150	165	110	83	66	44	33	26	22	17	13	11	8	7	5	4	3
164	184	123	92	74	49	37	29	25	18	15	12	9	7	6	5	4
238	270	180	135	108	72	54	43	36	27	22	18	14	11	8	7	5
340	399	266	200	160	106	80	64	53	40	32	27	20	16	12	10	8
360	425	284	213	170	113	85	68	57	43	34	28	21	17	13	11	9
363	424	283	212	170	113	85	68	57	42	34	28	21	17	13	11	8
435	524	349	262	209	140	105	84	70	52	42	35	26	21	16	13	10
665	*	540	405	324	216	162	130	108	81	65	54	40	32	25	20	16
700	*	571	428	342	228	171	137	114	86	68	57	43	34	26	21	17
850	*	*	526	421	281	211	168	140	105	84	70	53	42	32	26	21

FIG.-22

c. Kasicka et al.

Kasicka et al. ("Kasicka") teach away from the tight bending radius of the claimed invention. This reference, which was cited in the IDS for the instant application, quantitatively investigates the influence of capillary coiling on separation efficiency in capillary zone electrophoresis¹⁰. Kasicka concluded that it is preferred to perform capillary zone electrophoresis in straight, rather than coiled capillaries. Kasicka further concluded that due to the low diffusion coefficients, the separation efficiency in coiled capillaries is negatively impacted to a greater extent for large bioparticles, such as Tobacco Mosaic Virus than for very small analytes such as glycine. However, even for the analysis of glycine, these authors recommend a bend radius greater than 30 mm (3 cm). In contrast to Kasicka, it is hypothesized in Applicants' specification that coils actually help large molecules having a smaller diffusion coefficients travel to the wall of the open tubular capillary during the extraction process.

In summary, multiple references teach away from tightly coiled **open** fused silica capillaries having a bend radius of less than 3 cm. Additionally, capillaries having a bend radius of less than 3 cm are contrary to accepted wisdom in the art. Therefore, claims 1 and 2 are not obvious over the combination of Xiao and Henry. Since claims 7, 9, 11, 31, 34 and 35 depend from claims 1

¹⁰ Electrophoresis 1995, volume 16, pp 2034 – 2038.

or 2, they are not obvious over the combination of Xiao and Henry. Claim 8 was cancelled in the response dated October 20, 2008, rendering the rejection moot. In view of the foregoing, the withdrawal of the § 103 rejections is respectfully requested.

B. Xiao et al., Henry et al. and Smith et al.

Claim 10 was rejected under 35 U.S.C. 103(a) as being unpatentable over Xiao et al. in view of Henry et al. as applied to claims 1, 2, 7 - 9, 11, 31, 34, 35 and 38 and further in view of Smith et al. (US 4,569,794, "Smith"). Claim 10 recites an open fused silica capillary wherein at least some portion of the capillary is coiled at a bend radius of less than 3 cm and wherein the extraction surface comprises an immobilized metal ion. On page 4 of the Office action, the Examiner states that neither Xiao nor Henry disclose the use of metal ions to bind analytes. Therefore, the Examiner is relying on Henry to supply the capillaries having a bend radius of less than 3 cm. However, as Applicants argued above (in section A), the claimed invention is not obvious over Xiao and Henry because Xiao and Henry fail to teach a coiled **open** fused silica capillary having a **bend radius of less than 3 cm**.

Smith does not supply the missing teachings. Smith teaches a process for separating a biologically active polypeptide or protein using a resin containing immobilized metal ions¹¹. Smith does not teach coiled fused silica capillaries having a bend radius of less than 3 cm. Since none of the cited references teach **open** capillaries having a bend radius of less than 3 cm, claim 10 is not obvious over the combination Xiao, Henry and Smith. In view of the foregoing, withdrawal of the rejection is respectfully requested.

C. Xiao et al., Henry et al. and Kumar et al.

The Examiner rejected claims 15, 16, 32, 33, 36 and 37 under 35 U.S.C. 103(a) as being unpatentable over Xiao et al. in view of Henry et al. as applied to claims 1, 2, 7 - 9, 11, 31, 34, 35 and 38 and further in view of Kumar et al. (US 5,976,896, "Kumar"). The rejected claims are drawn to open fused silica capillaries wherein at least some portion of the capillary is coiled at a bend radius of less than 3 cm and wherein the capillaries are connected to a pump. On page 4 of the Office action, the Examiner states that neither Xiao nor Henry disclose the use of a syringe pump. Therefore, the Examiner is relying on Henry to supply coiled capillaries having a bend radius of less than 3 cm. However, as Applicants argued above (in section A), the claimed invention is not obvious

¹¹ Smith, abstract

over Xiao and Henry because the combination of Xiao and Henry fail to teach an **open** fused silica capillary coiled to **bend radius of less than 3 cm**.

Kumar does not supply the missing teachings. Kumar teaches a device for performing immunoassays in one or more capillary tubes. Kumar does not teach coiled capillaries. Kumar's capillaries are relatively short in length, typically between 1 and 15 cm¹² so coiling is not particularly necessary or advantageous. Since none of the cited references teach **open** capillaries having a bend radius of less than 3 cm, claims 15, 16, 32, 33, 36 and 37 are not obvious over the combination of Xiao, Henry and Kumar. In view of the foregoing, withdrawal of the rejections is respectfully requested.

¹² Kumar, column 14, lines 19 - 23.

CONCLUSION

Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

The Commissioner is hereby authorized to charge \$245 for a two-month extension of time to Deposit Account No. 50-2852. In the event that an extension of time is required in addition to that requested in the enclosed petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 50-2852.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (408)267-7214.

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